Antifungals, Oral
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s) for oral use
clotrimazole lozenge[1]	generic	▪ Treatment of oropharyngeal candidiasis ▪ To prophylactically reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation
fluconazole (Diflucan®)[2]	generic	▪ Treatment of oropharyngeal, esophageal, and vaginal candidiasis ▪ Treatment of *Candida* urinary tract infections, peritonitis, candida systemic infections including candidemia, disseminated candidiasis, and pneumonia ▪ Cryptococcal meningitis ▪ Prevention of candidiasis in patients undergoing bone marrow transplantation receiving cytotoxic chemotherapy and/or radiation
flucytosine (Ancobon®)[3]	generic	▪ Used in combination with amphotericin B for the treatment of serious infections caused by susceptible strains of *Candida* or *Cryptococcus*
griseofulvin suspension[4]	generic	▪ Ringworm infections of the body, skin, hair, and nails, namely tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, and tinea unguium (onychomycosis)
griseofulvin, microsized[5]	generic	
griseofulvin, ultramicrosized (Gris-PEG®)[6]	generic	
isavuconazonium (Cresemba)[7]	Astellas	▪ Azole antifungal for use in the treatment of invasive aspergillosis, and invasive mucormycosis in patients 18 years and older†
itraconazole (Onmel™)[8]	Merz	▪ Treatment of onychomycosis of the toenail caused by *Trichophyton rubrum*, or *T. mentagrophytes*
itraconazole (Sporanox®)[9]	generic	▪ Onychomycosis of the fingernail and/or toenail due to dermatophytes (tinea unguium) in non-immunocompromised patients ▪ Treatment in immunocompromised and non-immunocompromised patients with pulmonary and extrapulmonary blastomycosis, histoplasmosis; or patients with aspergillosis intolerant of amphotericin B; or aspergillosis refractory to amphotericin B
ketoconazole[10]	generic	▪ Blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, paracoccidioidomycosis, only in patients who are intolerant to, or who have failed, other agents*
miconazole (Oravig™)[11]	Par Pharmaceuticals	▪ Local treatment of oropharyngeal candidiasis (OPC) in adults
nystatin[12]	generic	▪ Gastrointestinal and oral candidiasis caused by *Candida albicans*
posaconazole (Noxafil®)[13]	Merck	▪ Delayed-release tablet and oral suspension: Prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years and older who are at high risk of developing these infections due to being severely immunocompromised (e.g., hematopoietic stem cell transplant recipient with graft versus host disease [GVHD] or those with hematologic malignancies with prolonged neutropenia from chemotherapy) ▪ Oral suspension: Treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.
terbinafine (Lamisil®)[14]	generic	▪ Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indication(s) for oral use
terbinafine (Lamisil® Granules)[15]	Novartis	▪ Treatment of tinea capitis in patients four years of age and older
voriconazole (Vfend®)[16]	generic	▪ Treatment of invasive aspergillosis ▪ Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy. ▪ Treatment of esophageal candidiasis ▪ Treatment of candidemia in non-neutropenic patients and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds

* Ketoconazole is no longer to be used as first-line therapy for any fungal infection and should be reserved for only those cases where alternative therapies are unavailable or not tolerated. Please revisit the indications section of the package insert for details. Previously, ketoconazole was indicated for candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, and severe recalcicant cutaneous dermatophyte infections not responding to topical or oral griseofulvin therapy. These indications were removed due to the risk of hepatic toxicity.[17]

^ fluconazole, isavuconazonium, posaconazole and voriconazole are also available in intravenous (IV) formulations.

*Terbinex (terbinafine) kit was discontinued in 2014.

OVERVIEW

The antifungal agents have different spectrums of activity and are FDA-approved to treat a variety of infections. Few trials have been performed to compare safety and efficacy profiles of the drugs. In addition, many of the agents carry black box warnings related to adverse events and/or drug interactions.

The Infectious Diseases Society of America (IDSA) 2009 guidelines on the treatment of oropharyngeal candidiasis in adults include clotrimazole troches (Mycelex) or nystatin for mild disease; for moderate to severe disease, fluconazole (Diflucan) is recommended (updated guidelines are projected to be published in the fall of 2015).[18] For fluconazole-refractory disease, itraconazole solution or posaconazole suspension (Noxafil) may be used. In other refractory cases, voriconazole (Vfend) or amphotericin B oral suspension may be administered. Chronic suppressive therapy for patients with human immunodeficiency virus (HIV) is not always necessary. If suppressive therapy is required, fluconazole is recommended.

Since highly active antiretroviral therapy (HAART) for the treatment of HIV for infants and children is widely available and utilized in the U.S., routine primary prophylaxis of candidiasis is not indicated.[19] Uncomplicated infections can be effectively treated with topical therapy such as clotrimazole troches or nystatin. Troches should not be used in infants. Systemic therapy with fluconazole, ketoconazole, or itraconazole may be considered for the initial treatment of oropharyngeal candidiasis. Fluconazole is more effective than nystatin for infants. Itraconazole has equivalent efficacy to fluconazole for oropharyngeal candidiasis, but it is less well tolerated. Ketoconazole absorption can be variable so it is recommended to use fluconazole or itraconazole solutions, when available.

For esophageal candidiasis in adults, fluconazole, oral or IV, is considered first line (next projected update is fall 2015).[20] Fluconazole or itraconazole are preferred for children for the management of esophageal candidiasis.[21] Posaconazole, itraconazole, or voriconazole may be used in patients with fluconazole-refractory infections.

Onychomycosis is a fungal infection of the nail bed (skin beneath the nail plate) with secondary involvement of the nail plate (visible part of the nail on fingers and toes). Dermatophytes, yeasts, and molds are the primary pathogens associated with onychomycosis. More common in toenails than fingernails, the disease often causes the end of the nail to separate from the nail bed. The most common clinical presentations are distal and lateral subungual onychomycosis (which usually affects the great or first toe) and white superficial onychomycosis (which generally involves the third or fourth toes).[22] Additionally, debris (white, green, yellow, or black) may build up under the nail plate and discolor the nail bed. Onychomycosis is often chronic, difficult to eradicate, has a tendency to recur, and is found more frequently in the elderly.

Opportunistic fungal infections are particularly likely to occur in patients during corticosteroid, immunosuppressant, or antimetabolite therapy, or in patients with Acquired Immunodeficiency Syndrome (AIDS), azotemia, diabetes mellitus, bronchiectasis, emphysema, tuberculosis, lymphoma, leukemia, or burns. histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis are systemic mycoses which can cause disease in both healthy and immunocompromised individuals. In contrast, mycoses caused by opportunistic fungi such as *Candida albicans, Aspergillus spp, Trichosporon, Torulopsis (Candida) glabrata, Fusarium, Alternaria*, and *Mucor* are generally found only in an immunocompromised host.

PHARMACOLOGY

Drug	Mechanism of Action
clotrimazole (Mycelex Troche)[23]	Inhibits the action of fungal ergosterol synthesis; interacts with the cytochrome P450 enzyme 14-alpha demethylase; inhibits growth of pathogenic yeasts by altering cell membrane permeability
fluconazole (Diflucan)[24]	Highly selective inhibitor of fungal cytochrome P450 sterol C-14 alpha-demethylase, which results in fungistatic activity
flucytosine (Ancobon)[25]	Enters the fungal cell and is metabolized to 5-fluorouracil, which is extensively incorporated into fungal RNA and inhibits synthesis of both DNA, RNA, and protein synthesis; the result is unbalanced growth and death of the fungal organism
griseofulvin[26]	Fungistatic amounts are deposited in the keratin precursor cell. The new keratin becomes resistant to fungal invasion.
isavuconazonium (Cresemba)[27]	Isavuconazonium sulfate is a prodrug of isavuconazole, which inhibits the synthesis of ergosterol within the fungal cell membrane via inhibition of the enzyme lanosterol 14-alpha-demethylase, which in turn is responsible for the conversion of lanosterol to ergosterol. This results in a weakening of the cell membrane function and structure.
itraconazole (Onmel)[28]	Inhibits the cytochrome P450-dependent synthesis of ergosterol, a vital component of fungal cell membranes.
itraconazole (Sporanox)[29]	Inhibits the cytochrome P450-dependent synthesis of ergosterol, a vital component of the fungal cell membrane, resulting in increased cellular permeability and therefore leakage of cellular contents
ketoconazole (Nizoral)[30]	Impairs the synthesis of ergosterol, a vital component of fungal cell membranes
miconazole (Oravig)[31]	Inhibits cytochrome P450-dependent 14-α demethylase in the biosynthetic pathway of ergosterol, an essential component of the fungal cell membrane.
nystatin[32]	Binds to sterols in the fungal cell membranes which leads to fungistatic activity
posaconazole (Noxafil)[33]	Inhibits cytochrome P450-dependent 14-α demethylase in the biosynthetic pathway of ergosterol which weakens the structure and function of the fungal cell membrane

Pharmacology (continued)

Drug	Mechanism of Action
terbinafine (Lamisil, Lamisil Granules)[34,35]	Inhibits squalene epoxidase, a key enzyme in fungal sterol biosynthesis; resulting in cell death due to increased cell membrane permeability; fungicidal in vitro depending on organism and concentration
voriconazole (Vfend)[36]	Inhibits ergosterol synthesis by interacting with the 14-alpha-lanosterol demethylation step, a cytochrome P450 enzyme

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-life (hr)	Metabolism	Excretion (%)	CYP 450 Enzyme Inhibition
clotrimazole (Mycelex Troche)[37]	negligible absorption	--	The small amount that is absorbed is metabolized by the liver	Bile	--
fluconazole (Diflucan)[38]	>90	20-50	--	Renal: 91	2C9, 3A4
flucytosine (Ancobon)[39]	78-89	2.4-4.8	Small amount of flucytosine is deaminated (probably by gut bacteria) to 5-fluorouracil and reabsorbed	Renal: 90 Fecal: <10	--
griseofulvin[40]	varies with formulation; absorption increases with a high-fat meal	9-24	No active metabolites	Renal , fecal and perspiration excretion	--
Isavuconazonium (Cresemba)[41]	98	130	Rapidly hydrolyzed into active drug	Renal: 45.6 Fecal: 46.1	3A4, 3A5
itraconazole (Onmel)[42]	63 Absorption increases with a high-fat meal	37	Several metabolites; hydroxyitraconazole is the major active one	Renal: 35 Fecal: 54	3A4
itraconazole (Sporanox)[43]	55	64	Several metabolites; hydroxy-itraconazole is the major active metabolite	Renal: 35 Fecal: 54	3A4
ketoconazole (Nizoral)[44]	-- (requires acidic pH)	8	Several inactive metabolites	Renal: 13 Bile: 87 (Fecal: 57)	3A4
miconazole (Oravig)[45]	--	24	No active metabolites	Renal: <1	2C9, 3A4
nystatin[46]	poorly absorbed	--	--	Predominantly feces	--

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Metabolism	Excretion (%)	CYP 450 Enzyme Inhibition
posaconazole (Noxafil)[47]	-- (suspension: varies based on fed or fasting state) 54 (tablet)	20-66 (suspension) 26-31 (tablet)	No active metabolites	Renal: 13 Fecal: 71	3A4
terbinafine (Lamisil)[48]	40	200-400	No active metabolites	Renal: 70	2D6
terbinafine (Lamisil Granules)[49]	--	9.3-13.8	No active metabolites	Renal: 70	2D6
voriconazole (Vfend)[50]	96	dose dependent	N-oxide metabolite is inactive; several other inactive metabolites	Renal: 80-83	2C19, 2C9,3A4

CONTRAINDICATIONS/WARNINGS

clotrimazole (Mycelex)

Clotrimazole is not indicated for systemic mycoses including systemic candidiasis.[51]

fluconazole (Diflucan)[52]

Fluconazole is contraindicated in patients with hypersensitivity to fluconazole or any of its excipients. There is no information regarding cross-hypersensitivity among fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles.

Fluconazole is associated with QT prolongation and is a moderate CYP3A4 inhibitor. Therefore, fluconazole is contraindicated with concurrent administration of drugs that prolong the QT interval and are metabolized via CYP3A4, such as quinidine and pimozide. Avoid concomitant administration of fluconazole and voriconazole, and fluconazole and erythromycin.

Fluconazole has been associated with rare reports of anaphylaxis, serious hepatic toxicity, and exfoliative skin disorders including Stevens-Johnson Syndrome and Toxic Epidural Necrosis during treatment. Discontinuation of the drug is recommended if skin reactions occur.

Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities, primarily in patients with serious underlying medical conditions. There has been no obvious relationship to total daily dose, duration of therapy, sex, or age of the patients in the known cases of fluconazole-associated hepatotoxicity. Fluconazole hepatotoxicity has usually, but not always, been reversible upon discontinuation. Patients with abnormal liver function tests during fluconazole therapy should be monitored for more severe hepatic injury. Discontinue fluconazole therapy if clinical signs and symptoms of liver disease develop during therapy.

flucytosine (Ancobon)

Flucytosine is excreted primarily by the kidneys, and renal impairment leads to accumulation of drug. There is a boxed warning associated with flucytosine to use extreme caution in patients with impaired renal function. Monitoring of renal, hepatic, and hematologic status is stressed to prevent progressive accumulation of active drug.[53] In addition, extreme caution in patients with bone marrow depression should be exercised.

griseofulvin (microsized, Gris-PEG)[54,55]

Griseofulvin is contraindicated in patients with porphyria, hepatocellular failure, and in patients with a history of hypersensitivity to griseofulvin.[56] Griseofulvin should not be prescribed to pregnant patients. If a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Since griseofulvin has demonstrated harmful effects *in vitro* on the genotype in bacteria, plants, and fungi, males should wait at least six months after completing griseofulvin therapy before fathering a child.

Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin, as well as exacerbating the condition of those with Systemic Lupus erythematosus (SLE) or lupus-like syndrome.

Photosensitivity skin reactions have been associated with griseofulvin therapy. Patients should be warned to avoid exposure to intense natural or artificial sunlight. Severe skin reactions, (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme), have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. If severe skin reactions occur, griseofulvin should be discontinued.

Elevated liver function tests and jaundice have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. Patients should be monitored for hepatic adverse events and discontinuation of griseofulvin considered, if warranted.

Griseofulvin is produced by a species of *Penicillium*; patients with penicillin hypersensitivity theoretically could exhibit a cross-sensitivity to griseofulvin. However, patients with penicillin hypersensitivity have been treated with griseofulvin without adverse affects. Similar warnings may apply to patients with cephalosporin hypersensitivity or carbapenem hypersensitivity because of the structural similarity of cephalosporins and carbapenems to penicillin.

Concomitant use of griseofulvin and oral contraceptives has been reported to reduce the efficacy of the oral contraceptive and cause breakthrough bleeding. Patients who experience breakthrough bleeding while receiving these drugs together should notify their prescribers. An alternate or additional form of contraception should be used during concomitant treatment and should be continued for one month after griseofulvin discontinuation. Additionally, patients taking non-oral combination contraceptives, estrogens, or progestins for hormone replacement therapy may also experience reduced clinical efficacy; dosage adjustments may be necessary.

isavuconazonium (Cresemba)[57]

Isavuconazonium is contraindicated in patients with hypersensitivity to isavuconazole. Do not use in the presence of strong CYP3A4 inhibitors or strong CYP3A4 inducers. Either can significantly increase or decrease plasma concentrations of isavuconazole.

Isavuconazole is known to shorten the QTc interval, therefore it is contraindicated in those adults with familial short QT syndrome.

Warnings for hepatic adverse drug reactions include; increases in ALT and AST that are generally reversible and do not require discontinuation. More severe hepatic reactions such as hepatitis, cholestatis, or liver failure including death have been reported in those patients with underlying medical conditions. Evaluate hepatic laboratory tests at baseline and during therapy. Discontinue drug if liver disease develops.

Fetal harm may occur when Cresemba is administered to pregnant females. Use in pregnancy only when the potential benefit outweighs risk to the fetus.

itraconazole (Sporanox, Onmel)[58,59]

Itraconazole should not be administered to women considering pregnancy or who are pregnant. Simvastatin and lovastatin, which are metabolized by CYP 3A4, are contraindicated with itraconazole. Itraconazole should not be administered with ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, and methylergometrine (methylergonovine). Additionally, co-administration with pimozide, quinidine, oral midazolam, cisapride, triazolam, lev-acetylmethadol (levomethadyl), and dofetilide are contraindicated as concomitant use may result in elevated plasma concentrations of those drugs leading to potentially serious adverse events.

Itraconazole is contraindicated in patients with ventricular dysfunction as evidenced by congestive heart failure (CHF) or a history of CHF. A black box warning associated with itraconazole stresses that itraconazole should not be used for onychomycosis in patients with evidence of ventricular dysfunction or CHF due to the risk of pulmonary edema and/or CHF. Negative inotropic effects have been observed with intravenous itraconazole. Serious cardiovascular events, including QTc prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred when itraconazole is co-administered with inhibitors of CYP450 3A4 isoenzyme. Such patients should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole, discontinue administration.

A black box warning regarding drug interactions is now included in the label. There is a list of drugs contraindicated in the presence of itraconazole (see interactions chart). Coadministration of any of these drugs with itraconazole can cause elevations of plasma concentrations thereby increasing or prolonging both the pharmacologic effects and/or the adverse reactions to the drugs. Do not use itraconazole in the presence of CYP3A4 substrates. For example; calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of itraconazole and nisoldipine is contraindicated.

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated. The hearing loss usually resolves when treatment is stopped but can persist in some patients.

Itraconazole capsules and oral solution should not be used interchangeably as the drug exposure is greater with the oral solution than with the capsules when the same dose of drug is administered. Only the oral solution has demonstrated efficacy for oral and/or esophageal candidiasis.

Serious hepatotoxicity, including liver failure and death, has been associated with itraconazole. Some patients did not have an underlying medical condition or pre-existing liver disease. Hepatotoxicity may develop as early as the first week of treatment. If signs or symptoms develop that are consistent with liver disease, itraconazole therapy should be discontinued and liver function testing performed.

Due to large pharmacokinetic variability in cystic fibrosis patients, consider switching to alternative antifungal therapy when the patient does not respond to itraconazole.

itraconazole (Sporanox) and terbinafine (Lamisil, Lamisil Granules)[60,61]

Both itraconazole and terbinafine prescribing information recommend, "Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis." A warning for both terbinafine and itraconazole states that neither agent should be used in patients with pre-existing liver disease, and rare cases of liver failure have occurred during use of either product.

ketoconazole (Nizoral)[62,63,64]

Ketoconazole should not be administered with terfenadine, astemizole, cisapride, or triazolam as concurrent administration has resulted in cardiovascular adverse events.

Ketoconazole tablets should only be used when other effective antifungal therapy is not available or tolerated. QT prolongation can occur if certain drugs are coadministered with ketoconazole (see interactions chart). The QT prolongation has resulted in life-threatening ventricular dysrhythmias such as torsades de pointes.

A black box warning states that ketoconazole has been linked to hepatic toxicities and fatalities. Use in patients with hepatic disease is contraindicated. The presence of viral hepatitis and liver function tests should be assessed prior to therapy, and monitoring of hepatic function is recommended weekly during therapy.

Adrenal insufficiency has also been reported due to the inhibition of production of corticosteroids. Monitor adrenal function in those patients with existing adrenal concerns while they are utilizing oral ketoconazole therapy.

A medication guide outlining the risks associated with oral ketoconazole use has been approved for distribution by the FDA.

miconazole (Oravig)[65]

Miconazole is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to miconazole, milk protein concentrate, or any other component of the product.

Allergic reactions, including anaphylactic reactions and hypersensitivity, have been reported with the administration of miconazole products, including Oravig. Discontinue miconazole immediately at the first sign of hypersensitivity.

nystatin[66]

Nystatin suspension contains significant amounts of sucrose; it should be used cautiously in patients with diabetes mellitus.

posaconazole (Noxafil)[67]

Posaconazole is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to posaconazole, any other component of the product, or hypersensitivity to any other azole antifungal. Posaconazole is contraindicated in coadministration with sirolimus (sirolimus toxicity) and ergot alkaloids (ergotism). Posaconazole is also contraindicated in coadministration with the CYP3A4 substrates, pimozide, halofantrine, or quinidine, since this may result in increased plasma concentrations of these agents leading to QTc prolongation and rare occurrences of torsades de pointes. Posaconazole is contraindicated with HMG-coA reductase inhibitors primarily metabolized through CYP3A4 due to risk of rhabdomyolysis.

Infrequent cases of hepatic reactions such as mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis have been reported with posaconazole. Liver enzyme elevations were generally reversible upon discontinuation or, in some cases, normalized without drug interruption, and rarely require drug discontinuation. More serious hepatic reactions including cholestasis or hepatic failure including fatalities have been reported in patients with serious underlying medical conditions, such as hematologic malignancy during treatment with posaconazole. Posaconazole 800 mg daily has been associated with the more severe hepatic reactions. Liver function tests should be evaluated at therapy initiation and during the course of posaconazole therapy. If abnormal liver function tests occur during posaconazole therapy, monitor for the development of more severe hepatic injury. Posaconazole should be discontinued if worsening of liver function tests continues.

Elevated cyclosporine levels resulting in rare serious adverse events including nephrotoxicity, leukoencephalopathy, and death were reported in clinical efficacy trials for posaconazole. Dose reduction and more frequent monitoring of cyclosporine and tacrolimus should be performed when posaconazole therapy is initiated.

Posaconazole significantly increases the Cmax and AUC of tacrolimus. Reduce tacrolimus dose by approximately one-third of the original dose on initiation of posaconazole treatment. Frequent monitoring of tacrolimus trough concentrations should be performed during and at discontinuation of posaconazole treatment.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

Posaconazole has been known to prolong the sedative/hypnotic effects of midazolam, the serum concentration of midazolam may be increased five fold. Monitor those patients taking concomitant midazolam. In the event signs or symptoms of prolonged hypnosis/sedation signs are noted, have benzodiazepine receptor antagonists available for administration.

terbinafine (Lamisil, Lamisil Granules)[68,69]

Terbinafine is contraindicated in patients with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis.

Severe hepatic injury, including liver failure, with some leading to death or liver transplantation, has occurred with the use of oral terbinafine. Assessment of serum transaminases are advised before

initiation of treatment with terbinafine. Terbinafine should be discontinued if biochemical or clinical evidence of liver injury occurs.

Severe neutropenia has been reported, if neutrophil count is $\leq$ 1,000 cells/mm^3, discontinue drug. Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with terbinafine use as has erythema multiforme, exfoliative dermatitis, and bullous dermatitis. If a progressive skin rash occurs, treatment with terbinafine should be discontinued. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) has also been reported. Depressive symptoms have been reported with terbinafine, physicians should be alerted to the development of depressive symptoms.

Taste disturbance, including taste loss, has been reported with the use of terbinafine. Taste disturbances can be severe enough to result in decreased food intake, weight loss, and depressive symptoms. Resolution of taste disturbance may resolve within several weeks after discontinuation of treatment, but may be prolonged (greater than one year), or permanent. If symptoms of a taste disturbance occur, discontinue terbinafine.

In addition, smell disturbance and loss of smell has been reported. The changes may resolve after discontinuation of treatment but may be prolonged and possibly permanent. If symptoms of a smell disturbance occur, discontinue use.

voriconazole (Vfend)[70]

Coadministration of voriconazole is contraindicated with CYP3A4 substrates including terfenadine, astemizole, cisapride, pimozide, quinidine, rifabutin, sirolimus, or ergot alkaloids because increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of torsades de pointes. Voriconazole use with efavirenz 400 mg every 24 hours or higher is contraindicated. Voriconazole should not be given concurrently with sirolimus (increased sirolimus concentrations and decreased voriconazole concentration), rifampin, carbamazepine, and long-acting barbiturates (decreased voriconazole concentrations), high-dose ritonavir 400 mg every 12 hours (decreased voriconazole concentrations), ergotamines, and St. John's Wort. Additionally, voriconazole should not be given with rifabutin as voriconazole concentrations are decreased, and rifabutin concentrations are increased. Ergot alkaloids should not be used with voriconazole.

Concurrent administration of oral voriconazole and oral fluconazole has shown to result in an increase in Cmax and AUC of voriconazole by an average of 57 and 79 percent, respectively. Reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or decrease this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 hours of the last dose of fluconazole.

Voriconazole prescribing information should be consulted for a detailed description of drug interactions and required dosage modifications prior to initiating therapy. Monitoring liver enzymes before and during therapy is recommended. Visual disturbances (including optic neuritis and pailledema) associated with therapy have not been studied beyond 28 days. Monitor visual function if therapy continues beyond 28 days. Electrolyte disturbances including hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation of therapy with voriconazole as electrolyte disturbances increase the risk of cardiac arrhythmias.

As with other azole antifungals, hypersensitivity to voriconazole or any of the excipients contraindicates its use. There is no information regarding cross-sensitivity among voriconazole and other azole antifungal agents.

Voriconazole is associated with rare cases of serious hepatic reactions including clinical hepatitis, cholestasis, and fulminant hepatic failure with fatalities. Severe hepatic reactions have occurred in patients with serious underlying medical conditions, predominantly hematological malignancy. Hepatic reactions such as hepatitis and jaundice have occurred in patients with no identifiable risk factors. Liver dysfunction was reversible after discontinuation of voriconazole in most cases. Liver function tests should be performed prior to voriconazole therapy and during therapy to monitor for hepatic injury.

Voriconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Embryo-fetal toxicity can occur; do not administer to pregnant women unless the benefit to the mother outweighs the risk to the fetus.

Discontinue drug use for exfoliative cutaneous reactions. Avoid sunlight due to risk of photosensitivity.

Skeletal events such as fluorosis and periostitis have occurred with long-term voriconazole therapy. Discontinue use if these events occur.

DRUG INTERACTIONS

Numerous drug interactions are associated with antifungal agents. See chart on next page.

Due to low systemic absorption, drug interactions with clotrimazole and nystatin are limited.[71,72]

Clotrimazole is an inhibitor of hepatic cytochrome P450 (CYP) 3A4, and tacrolimus is metabolized by CYP3A4.[73,74] Administration of clotrimazole troches to renal transplant patients receiving tacrolimus caused clinically significant increases in the relative oral bioavailability, Tmax, and trough concentrations of tacrolimus.[75,76] Tacrolimus blood concentrations should be monitored closely whenever clotrimazole therapy is initiated or discontinued. Close monitoring can minimize toxicity due to increased tacrolimus levels or prevent an acute rejection episode due to subtherapeutic tacrolimus levels.

Isavuconazonium follows other azole antifungals in that use with strong CYP3A4 inhibitors or inducers is contraindicated as concomitant use can significantly increase/decrease isavuconazole concentrations.[77]

Flucytosine can cause significant hematologic toxicity. It should be used cautiously with all antineoplastic agents, especially those that cause bone marrow depression. Cytarabine can competitively inhibit flucytosine, antagonizing its antifungal activity. Other bone marrow depressants include carbamazepine, clozapine, phenothiazines, zidovudine, and other blood dyscrasia-causing medications.

Posaconazole (Noxafil) is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux.[78] Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. The UDP inducers include efavirenz, rifabutin, and phenytoin. The UDP inducers reduce Cmax and area under the curve (AUC) of posaconazole thus reducing bioavailability. Avoid concurrent use with efavirenz, phenytoin, rifabutin,

or cimetidine unless the benefit outweighs the risks. Frequent monitoring of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration with posaconazole.

In patients taking both posaconazole and digoxin, increased plasma concentrations of digoxin have been noted. Monitor digoxin plasma concentrations of patients taking both agents concomitantly.

While some medications that are metabolized through the CYP3A4 system have specific contra-indications, any medication that is metabolized through this pathway and is taken concurrently with posaconazole should be monitored for adverse effects and toxicity. Dose adjustment may need to be considered.

Patients should be monitored for breakthrough fungal infections while on posaconazole when concurrently taking esomeprazole or cimetidine (due to an increase in gastric pH), as well as metoclopramide (due to an increase in gastrointestinal motility). Esomeprazole and metoclopramide have each shown to reduce Cmax and AUC of posaconazole. Avoid concurrent administration of posaconazole oral suspension with esomeprazole unless the benefit outweighs the risks. Other PPIs have not been studied in combination with posaconazole. The drug interactions with esomeprazole and metoclopramide do not apply to posaconazole delayed-release tablets. There are no drug interactions or dosage adjustments needed when posaconazole delayed-release tablets are concomitantly used with antacids, H2-receptor antagonists, and proton pump inhibitors.

No clinically relevant effect on posaconazole bioavailability and/or plasma concentrations was observed when administered with an antacid, glipizide, ritonavir, loperamide, or H2-receptor antagonists other than cimetidine; therefore, no posaconazole dose adjustments are required when used concomitantly with these products.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin.[79] Fentanyl plasma concentrations could be increased or exposure prolonged by concomitant use of itraconazole and may cause potentially fatal respiratory depression.

Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, methadone, lev-acetylmethadol (levomethadyl), or quinidine, concomitantly with itraconazole and/or other CYP3A4 inhibitors. Coadministration of cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, lev-acetylmethadol (levomethadyl), lovastatin, simvastatin, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine), or methadone with itraconazole capsules or oral solution is contraindicated.

Ketoconazole is a strong inhibitor of the CYP3A4 system. Due to this, use of this agent is contraindicated with certain other drugs that are metabolized by CYP3A4.

Concomitant administration of miconazole (Oravig) and warfarin has resulted in enhancement of anticoagulant effect. Cases of bleeding and bruising following the concomitant use of warfarin and topical, intravaginal, or oral miconazole were reported. Closely monitor prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests if miconazole is administered concomitantly with warfarin. Also monitor for evidence of bleeding.[80]

Although the systemic absorption of miconazole following miconazole (Oravig) administration is minimal and plasma concentrations of miconazole are substantially lower than when given

intravenously, the potential for interaction with drugs metabolized through CYP2C9 and CYP3A4, such as oral hypoglycemics, phenytoin, or ergot alkaloids, cannot be ruled out.

Voriconazole requires dose adjustment in the presence of CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers. Monitor for adverse reactions or lack of response. Increase the dose when concurrent use of phenytoin or efavirenz occurs.

Below is a list of common substrates for CYP 450 enzymes affected by oral antifungal agents:

- **Selected substrates for the 2C9 system:** diazepam, phenytoin, S-warfarin
- **Selected substrates for the 2C19 system:** phenytoin, thioridazine
- **Selected substrates for the 2D6 system:** carvedilol, clozapine, cyclobenzaprine, donepezil, flecainide, fluphenazine, fluoxetine, galantamine, haloperidol, hydrocodone, maprotiline, meperidine, methadone, methamphetamine, metoprolol, mexiletine, morphine, paroxetine, perphenazine, propafenone, propranolol, risperidone, thioridazine, timolol, tramadol, trazodone, and venlafaxine
- **Selected substrates for the 3A4 system:** triazolam, alprazolam, diazepam, atorvastatin, lovastatin, simvastatin, cyclosporine, tacrolimus, buspirone and pimozide

Drug Interactions Table

Consult package inserts for detailed information.

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
fluconazole (Diflucan)[81]	2C9, 3A4	erythromycin pimozide quinidine verapamil voriconazole - Avoid concurrent use	renal impairment rifampin celecoxib tacrolimus midazolam triazolam	cyclosporine Diflucan warfarin phenytoin sulfonylureas theophylline
flucytosine (Ancobon)[82]	--	--	renal impairment; drugs which reduce GFR	anti-neoplastic agents bone marrow suppressants
griseofulvin (Grifulvin V, Gris-PEG)[83,84]	--	--	barbiturates	warfarin cyclosporine tretinoin, ATRA sunitinib nilotinib

Drug Interactions Table (continued)

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
Isavuconazonium (Cresemba)[85]	3A4	Strong CYP3A4 inducers and inhibitors	Concurrent use is contraindicated	See package insert
itraconazole (Sporanox, Onmel)86,87	3A4	cisapride colchicine disopyramide dofetilide dronedarone eplerenone ergot alkaloids felodipine festoterodine irinotecan levomethadyl lovastatin lurasidone methadone oral midazolam nisoldipine pimozide quinidine ranolazine simvastatin solifenacin telithromycin ticagrelor triazolam	Decreases elimination of drugs metabolized by CYP3A4; dosing modification is required See package insert for complete detailed drug list	See package insert for full details
ketoconazole (Nizoral)[88]	3A4	alprazolam cisapride dofetilide eplerenone ergot alkaloids HMG-CoA reductase inhibitors isoniazid midazolam nisoldipine pimozide quinidine rifampin triazolam	cyclosporine methylprednisolone tacrolimus See package insert for detailed drug list	digoxin phenytoin sulfonylureas warfarin See package insert for full details
miconazole (Oravig)[89]	2C9, 3A4	--	--	ergot alkaloids oral hypoglycemic phenytoin warfarin

Drug Interactions Table (continued)

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
posaconazole (Noxafil)[90]	3A4	cimetidine* efavirenz* ergot alkaloids esomeprazole*(suspension) halofantrine HMG-CoA reductase inhibitors phenytoin* pimozide quinidine rifabutin* sirolimus	vinca alkaloids calcium channel blockers (3A4 inhibitors) cyclosporine tacrolimus midazolam phenytoin	atazanavir cyclosporine digoxin metoclopramide midazolam ritonavir tacrolimus
terbinafine (Lamisil, Lamisil Granules)[91]	2D6	thioridazine	TCAs SSRIs beta-blockers monoamine oxidase inhibitors–type b rifampin	caffeine cimetidine cyclosporine fluconazole theophylline warfarin
voriconazole (Vfend)[92]	2C19, 2C9,3A4	carbamazepine diflucan (avoid concurrent use) ergot alkaloids long-acting barbiturates pimozide quinidine rifabutin rifampin ritonavir (high dose) sirolimus St. John's Wort	alfentanil benzodiazepines (midazolam, triazolam, alprazolam) calcium channel blockers cyclosporine efavirenz methadone NSAIDS omeprazole phenytoin statins (3A4 inhibitors) tacrolimus vinca alkaloids	coumarin derivatives Diflucan fentanyl non-nucleoside reverse transcriptase inhibitors oral contraceptives with ethinyl estradiol and norethindrone oxycodone and other long acting narcotic analgesics protease inhibitors ritonavir (low-dose) sulfonylureas warfarin

*Avoid concomitant use unless benefits outweigh the risks

ADVERSE EFFECTS

Drug	Nausea	Headache	Rash	Vomiting	Abd. Pain	Diarrhea	Pruritus	Elevated LFT
clotrimazole (Mycelex troche)[93]	reported	nr	nr	reported	nr	nr	reported	15
fluconazole (Diflucan)[94] n=4,048	3.7	1.9	1.8	1.7	1.7	1.5	nr	reported
flucytosine (Ancobon)[95]	reported	reported	reported	reported	reported	reported	reported	reported
griseofulvin (microsized, Gris-PEG)[96, 97]	reported	reported	reported	reported	nr	reported	nr	reported
isavuconazonium (Cresemba)[98]	27.6	16.7	8.6	24.9	16.7	23.7	8.2	17.1
itraconazole (Onmel)[99]	reported	reported	nr	reported	reported	reported	nr	reported
itraconazole (Sporanox)[100] n=112 200 mg daily X 12 wks	3	10	3-4	reported	4	4	reported	4
ketoconazole (Nizoral)[101]	3	<1	nr	3	1.2	< 1	1.5	reported
miconazole (Oravig)[102]	0.7-6.6	5-7.6	nr	0.7-3.8	1.4-2.5	6-9	nr	nr
nystatin [103]	reported	nr	nr	reported	reported	reported	nr	nr
posaconazole suspension (Noxafil)[104] fluconazole (oral pharyngeal candidiasis)	9-29 11	8-20 9	3-15 4	7-28 7	5-18 6	10-29 13	nr	3-6 5-10
posaconazole delayed-release tablet (Noxafil)[105] (antifungal prophylaxis)	56	30	34	28	23	61	nr	reported
terbinafine (Lamisil)[106] n=465	2.6	12.9	5.6	reported	2.4	5.6	2.8	3.3
terbinafine (Lamisil Granules)[107] n=1,042	2	7	2	5	2	3	1	nr
voriconazole (Vfend)[108] n=1,655	5.4	3	5.3-7	4.4	< 2	< 2	< 2	1.8-12.4

Incidence is reported as a percentage. Adverse events data are obtained from prescribing information and therefore should not be considered comparative or all inclusive. Incidences for placebo indicated in parentheses. nr = not reported

Pyrexia at a rate of 59 percent has been reported with posaconazole delayed-release tablets.[109]

Voriconazole is reported to be associated with abnormal visual disturbances (21 percent IV and oral therapy) which resolve with discontinuation of therapy. Fever, chills, tachycardia, and hallucinations are also noted as common adverse reactions.[110]

In patients with normal gastrointestinal, renal, and hematologic function, flucytosine is generally associated with few adverse events, although rash, gastrointestinal discomfort, diarrhea (five to 10 percent), and reversible elevations in hepatic enzymes are occasionally observed. In patients with renal dysfunction or in patients on concomitant amphotericin B, leukopenia, thrombocytopenia, and enterocolitis may occur. Flucytosine is associated with dose-dependent, potentially lethal bone marrow suppression.[111]

Itraconazole (Onmel) has been associated with rare cases of hepatoxicity including liver failure and death.

Terbinafine tablets have been reported to be associated with taste disturbance and flatulence along with those adverse reactions listed in the table.

Terbinafine granules have been associated with nasopharyngitis, pyrexia, cough, and upper respiratory tract infections as well as those reported in the table.

SPECIAL POPULATIONS[112,113,114,115,116,117,118,119,120,121,122,129]

Pediatrics

Clotrimazole (Mycelex) troches have been used in children ages three years and older. Nystatin has been used in infants.[123] Terbinafine (Lamisil Granules) is approved for the treatment of tinea capitis for ages four years and older. The safety and efficacy of terbinafine tablets (Lamisil) have not been established in pediatric patients.

Safety and effectiveness of griseofulvin (Gris-Peg, Grifulvin V) have been established for children over age two years. Fluconazole safety and effectiveness data exist for children older than six months. Intravenous fluconazole has been used in preterm infants; however, efficacy has not been established in infants less than six months of age.[124]

Safety and effectiveness of posaconazole (Noxafil) oral suspension and delayed-release tablets in pediatric patients less than 13 years of age have not been established. Safety and effectiveness of itraconazole have not been proven in pediatric patients; however, patients aged six months to 16 years have been treated with itraconazole with no serious unexpected adverse events. Voriconazole (Vfend) does not have safety and effectiveness data in children less than 12 years old. Pharmacokinetics and safety data were collected in a small trial with intravenous voriconazole in children ages two to 11 years.[125]

Safety and efficacy of isavuconazonium (Cresemba) has not been studied in persons under age 18 years.[126]

No studies of flucytosine (Ancobon) in pediatric patients exist; however, published reports of use of flucytosine with and without amphotericin B in doses of 25-200 mg/kg per day are available. No unexpected serious adverse effects were reported.

Ketoconazole (Nizoral) tablets have not been studied in children of any age. The oral tablets should not be used in pediatric patients unless the benefits outweigh the risks.

Safety and effectiveness of miconazole (Oravig) in pediatric patients less than the age of 16 years have not been established. The ability of pediatric patients to comply with the application instructions has not been evaluated. Use in younger children is not recommended due to potential risk of choking.

Safety and efficacy in patients less than 12 years has not been established for voriconazole.

Pregnancy

Terbinafine is Pregnancy Category B. Clotrimazole, flucytosine, posaconazole, fluconazole, itraconazole, ketoconazole, nystatin, miconazole (Oravig), and griseofulvin are Pregnancy Category C. Voriconazole is Pregnancy Category D. Itraconazole (Sporanox) has received reports of congenital abnormalities in post-marketing experience. Only use during pregnancy if the potential benefit outweighs fetal risk.

Posaconazole, itraconazole (Onmel), and miconazole (Oravig) may cause fetal harm as has been shown in animal data. Nursing mothers should discontinue either nursing or the drug based on importance of the drug to the mother.

Two cases of conjoined twins have been reported with first trimester use of griseofulvin. Griseofulvin should not be used in pregnant patients. Griseofulvin therapy should be discontinued if the patient becomes pregnant during treatment, and potential hazards to the fetus should be explained.

The FDA issued a safety announcement regarding the use of long-term, high-dose (400 mg-800 mg/day) fluconazole during the first three months of pregnancy (first trimester) may be associated with a rare and distinct set of birth defects in infants. This risk is not associated with a single, low dose fluconazole 150 mg to treat vaginal yeast infection (candidiasis). The FDA categorizes a single 150 mg dose of fluconazole as category C but changed the Pregnancy Category for the use of fluconazole other than for vaginal candidiasis to category D.[127]

Isavuconazonium is a pregnancy category C drug. Sound clinical studies have not been conducted in this population, however based on animal studies isavuconazole may cause fetal harm when administered to pregnant women. It is recommended that this agent be used in pregnant women only when the potential benefit outweighs the risk to the fetus. If a woman becomes pregnant while on thereapy; she should consult her physician. This drug is not recommended for use while breastfeeding as the drug is excreted in the breastmilk of rats.[128]

Elderly

Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated.

No dose adjustment needed in the elderly for isavuconazonium (Cresemba). Pharmacokinetics remained unchanged between the younger adults (18-64yrs) and elderly (≥65yrs) population.

Hepatic Impairment

For patients with mild to moderate cirrhosis (Child-Pugh Class A and B), use the standard loading dose regimens of voriconazole; however, reduce the maintenance dose of voriconazole by one-half.

There is limited data available with itraconazole (Onmel) tablets in patients with hepatic impairment, therefore use with caution.

Isavuconazonium does not require dose adjustment with mild or moderate hepatic impairment, but has not been studied in the presence of severe liver impairment, therefore use with caution in patients who have a Child-Pugh Class C rating.

Itraconazole has been associated with rare cases off hepatotoxicity, including liver failure and death. In some instances, there was no history of pre-existing liver disease nor any other serious underlying medical conditions. Additionally, some of these cases developed within the first week of treatment. In the event any clinical signs or symptoms develop consistent with liver disease, discontinue drug and conduct liver function testing.

Ketoconazole oral therapy is contraindicated in persons with hepatic impairment. Assess and monitor patients for new and/or worsening of hepatic damage at baseline and weekly during therapy.

In the presence of mild to moderate hepatic impairment, voriconazole dosing should be half of the usual maintenance dose.

Renal Impairment

Monitor posaconazole oral suspension and delayed-release tablets closely for breakthrough fungal infections in those patients with severe renal impairment.

There is limited data available with itraconazole (Onmel) tablets with patients with renal impairment, therefore use with caution.

Do not administer voriconazole IV to patients with moderate to severe renal impairment (CrCl <50 mL/min).

No dose adjustment of isavuconazonium needed in patients with mild, moderate, severe, or end stage renal disease (ESRD).

Fluconazole is excreted renally as unchanged drug, there is no need to dose adjust with single dose therapy for vaginal candidiasis, but for renally impaired persons who will receive multiple doses, an initial loading dose of 50 to 400 mg should be administered followed by a daily dose based on creatinine clearance. Patients on dialysis should be administered 100 percent of the recommended dose after each session. On non-dialysis days, administer the dose based on creatinine clearance.

DOSAGES

Drug	Oral Dosage Forms	Adult Dosage
clotrimazole (Mycelex Troche)[129]	10 mg troche	▪ Treatment: One troche (10 mg) five times per day for 14 consecutive days ▪ Prophylaxis: One troche (10 mg) three times per day
fluconazole (Diflucan)[130]	50, 100, 150, 200 mg tablets 10 mg/mL, 40 mg/mL suspension	▪ Oropharyngeal and esophageal candidiasis: 200 mg X 1, then 100 mg daily ▪ Vaginal candidiasis: 150 mg orally X 1 ▪ Urinary tract infections and peritonitis: 50 to 200 mg daily ▪ Cryptococcal meningitis: 400 mg X 1, then 200 mg daily ▪ Undergoing bone marrow transplant: 400 mg daily until neutrophils >1,000 cells/m^3 for seven days ▪ Renal impairment for multiple dosing based on creatinine clearance. Loading dose of 50 – 400mg followed by; ▪ Creatinine Clearance >50 = 100% recommended dose ▪ CrCl ≤50 (no dialysis) = 50% of recommended dose ▪ CrCl ≤50 (dialysis session) = 100% recommended dose
flucytosine (Ancobon)[131]	250, 500 mg capsules	▪ 50 – 150 mg/kg/day in divided doses every six hours
griseofulvin (Grifulvin V, Gris-PEG)[132,133]	Microsized: Grifulvin V: 125 mg/5 mL suspension; 250, 500 mg tablets Ultramicrosized: Gris-PEG: 125, 250 mg tablets	Microsized: ▪ Onychomycosis: 1 g orally once a day for at least four months (fingernails) or at least six months (toenails) ▪ Tinea barbae: 500 to 1,000 mg orally once a day until infection has cleared ▪ Tinea capitis: 500 mg orally once a day for four to six weeks ▪ Tinea corporis: 500 mg orally once a day for two to four weeks ▪ Tinea cruris: 500 mg orally once a day until infection has cleared ▪ Tinea pedis: 1 g orally once a day for four to eight weeks Ultramicrosized: ▪ Onychomycosis : 750 mg orally in divided doses for at least four months (fingernails) or at least six months (toenails) ▪ Tinea barbae: 375 mg orally once a day or 375 to 750 mg in divided doses until infection has cleared ▪ Tinea capitis: 375 mg orally once a day or in divided doses for four to six weeks ▪ Tinea corporis: 375 mg orally once a day or in divided doses for two to four weeks ▪ Tinea cruris: 375 mg orally once a day or in divided doses until infection has cleared ▪ Tinea pedis: 750 mg orally in divided doses for four to eight weeks

Dosages (continued)

Drug	Oral Dosage Forms	Adult Dosage
isavuconazonium (Cresemba)[134]	186mg capsule (equiv to 100mg isavuconazole) 372mg vial for IV infusion (equiv to 200mg isavuconazole)	▪ Take 2 capsules orally every 8 hours for a total of 6 doses (48 hours) as a loading dose, then take 2 capsules once daily. With or without food. Swallow whole, do not chew or crush. ▪ Infuse 1 reconstituted vial every 8 hours for 6 doses (48 hours) as a loading dose, then infuse 1 reconstituted vial daily. *for both oral and IV forms; start the maintenance dose 12 – 24 hours after the last loading dose. **switching between oral and IV is acceptable and does not require a repeat loading dose.
itraconazole (Onmel)[135]	200 mg tablet	▪ Onychomycosis of the toenail: single 200 mg tablet orally once daily for 12 consecutive weeks. Take with a full meal at the same time each day.
itraconazole (Sporanox)[136]	100 mg capsule 10 mg/mL solution	▪ Onychomycosis (toenail): 200 mg daily for 12 weeks ▪ Onychomycosis (fingernail): two treatment pulses, which consist of 200 mg twice daily for one week. The pulses are separated by a three-week period without itraconazole. ▪ Treatment of Blastomycosis or Histoplasmosis: 200 mg once daily. If no evidence of improvement or progressing disease, the dose can be increased by 100 mg, up to 400 mg daily. Doses greater than 200 mg should be given in two divided doses. ▪ Treatment of life threatening situations should include a loading dose of 200 mg three times daily for the first three days. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate active fungal infection has subsided. ▪ Treatment of Aspergillosis: 200 to 400 mg daily ▪ Take the capsules with a full meal, swallow whole.
ketoconazole (Nizoral)[137]	200 mg tablet	▪ 200 to 400 mg daily
miconazole (Oravig)[138]	50 mg buccal tablets	▪ One 50 mg buccal tablet to the upper gum region (canine fossa) once daily for 14 consecutive days. Buccal tablet is applied after brushing teeth in the morning. Alternate gum site each day. ▪ Note: ▪ If the buccal tablet does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately. If the tablet still does not adhere, a new tablet should be placed. If the buccal tablet is swallowed within the first 6 hours, the patient should drink a glass of water and a new tablet should be applied only once. If the buccal tablet falls off or is swallowed after it was in place for 6 hours or more, a new tablet should not be applied until the next regularly scheduled dose. ▪ Chewing gum should be avoided. ▪ Do not chew, crush, or swallow the tablets.

Dosages (continued)

Drug	Oral Dosage Forms	Adult Dosage
nystatin[139,140,141]	Variety of dosage forms and strengths First Duke's mouthwash compounding kit consists of nystatin, diphenhydramine, and hydrocortisone. First Mary's mouthwash compounding kit consists of nystatin, diphenhydramine, tetracycline, and hydrocortisone.	▪ Gastrointestinal candidiasis: – 500,000 to 1,000,000 units three times daily ▪ Oral candidiasis: – 400,000 to 600,000 units four times daily
posaconazole (Noxafil)[142]	40 mg/1 mL oral suspension 100 mg delayed-release tablet	▪ Prophylaxis of invasive fungal Infections: Oral suspension: 200 mg (5 mL) three times daily during or immediately following (within 20 minutes) a full meal or with a liquid nutritional supplement or with an acidic carbonated beverage in patients who can not eat a full meal. For patients who cannot eat nor tolerate a supplement or an acidic carbonated beverage, alternative therapy should be considered. ▪ Delayed-release tablets: Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day. Maintenance dose of 300 mg (three 100 mg tablets) once a day, starting on the second day. Tablets should be taken with food to enhance oral absorption. The tabs provide higher plasma drug exposure than does the suspension under both fed and fasted conditions, therefore the table form is the preferred oral formulation. ▪ For both dosage forms, duration of therapy is based on recovery from neutropenia or immunosuppression. ▪ Oropharyngeal candidiasis: Loading dose of 100 mg (2.5 mL) twice daily on day 1 then 100 mg once daily for 13 days. ▪ Oropharyngeal candidiasis refractory to fluconazole and/or itraconazole: 400 mg (10 mL) twice daily. Duration to be determined by patient's severity of underlying disease and clinical response.
terbinafine (Lamisil)[143]	250 mg tablet	▪ Onychomycosis (toenail): 250 mg daily for 12 weeks ▪ Onychomycosis (fingernail): 250 mg daily for six weeks

Dosages (continued)

Drug	Oral Dosage Forms	Adult Dosage
voriconazole (Vfend)[144]	50, 200 mg tablets 40 mg/mL suspension 10 mg/mL injection	IV: (IV load is required to initiate therapy for all infections except esophageal candidiasis) ▪ Invasive Aspergillosis or Scedosporiosis or Fusariosis: 6 mg/kg every 12 hours for the first 24 hours, then 4 mg/kg every 12 hours ▪ Candidemia in nonneutropenics and other deep tissue candida infections: 6mg/kg every 12 hours for the first 24 hours, then 3-4 mg/kg every 12 hours thereafter. ▪ Oral: > 40 kg: 200 mg every 12 hours; may incease to 300 mg every 12 hours if response is inadequate < 40 kg: 100 mg every 12 hours; ; may incease to 150 mg every 12 hours if response is inadequate ▪ Concurrent phenytoin therapy: IV: 5 mg/kg every 12 hours Oral: > 40 kg: 400 mg every 12 hours < 40 kg: 200 mg every 12 hours Oral voriconazole should be taken one hour before or one hour after a meal.

Dosage recommendations for pediatric patients are listed below:

<table>
<tr><th>Drug</th><th>Oral Dosage Forms</th><th>Ages</th><th>Pediatric Dosage</th></tr>
<tr><td>clotrimazole (Mycelex Troche)[145]</td><td>10 mg troche</td><td>> three years</td><td>▪ Oropharyngeal candidiasis:
One troche (10 mg) five times per day</td></tr>
<tr><td>fluconazole (Diflucan)[146]</td><td>50, 100, 150, 200 mg tablets
10 mg/mL, 40 mg/mL suspension</td><td>six months to 13 years</td><td>▪ Oropharyngeal candidiasis: 6mg/kg X 1; then 3 mg/kg daily for at least two weeks
▪ Esophageal candidiasis: 6 mg/kg X 1; then 3 mg/kg daily for at least three weeks
▪ Cryptococcal meningitis: 12 mg/kg X 1; then 6 to 12 mg/kg daily
▪ Systemic infections: 6 to 12 mg/kg daily
▪ Equivalent dosing
<table>
<tr><th>Pediatric dose</th><th>Adult dose</th></tr>
<tr><td>3 mg/kg daily</td><td>100 mg daily</td></tr>
<tr><td>6 mg/kg daily</td><td>200 mg daily</td></tr>
<tr><td>12 mg/kg daily</td><td>400 mg daily</td></tr>
</table>
Pediatric dose should not exceed 600 mg daily.</td></tr>
<tr><td>griseofulvin (microsized, Gris-PEG)[147,148,149]</td><td>Microsized:
microsized:
125 mg/5 mL suspension;
250, 500 mg tablets
Ultramicrosized:
Gris-PEG: 125, 250 mg tablets</td><td>> two years</td><td>Microsized:
▪ Pediatrics: 10-20 mg/kg daily (max: 1 g) given in one to two divided doses
▪ Children weighing 30 to 50 pounds – 125 mg to 250 mg daily
▪ Children weighing over 50 pounds – 250 mg to 500 mg daily

Ultramicrosized:
▪ Pediatrics: 3.3-7.3 mg/kg/day
▪ Children weighing 35-60 pounds – 125 mg to 187.5 mg daily
▪ Pediatric patients weighing over 60 pounds – 187.5 mg to 375 mg daily</td></tr>
<tr><td>ketoconazole (Nizoral)[150]</td><td>200 mg tablet</td><td>> two years</td><td>▪ 3.3-6.6 mg/kg/day</td></tr>
<tr><td>nystatin[151]</td><td>various</td><td>neonates and older</td><td>▪ Oral candidiasis:
100,000 to 600,000 units four times daily</td></tr>
<tr><td>terbinafine (Lamisil Granules)[152]</td><td>125 mg packet
187.5 mg packet</td><td>> four years</td><td>▪ Tinea capitis:
Dose, based on body weight, given once daily for six weeks:
<table>
<tr><td>< 25 kg</td><td>125 mg</td></tr>
<tr><td>25-35 kg</td><td>187.5 mg</td></tr>
<tr><td>> 35 kg</td><td>250 mg</td></tr>
</table>
Sprinkle contents of pack on a spoonful of pudding or other soft non-acidic food such as mashed potatoes. Do not use apple sauce or fruit-based foods. Swallow entire spoonful without chewing. Take with food.</td></tr>
</table>

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials of oral agents used in the outpatient setting are considered the most relevant in this category. Many of the more recent studies have focused on inpatient use of the antifungal agents. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

fluconazole (Diflucan) and voriconazole (Vfend) – esophageal candidiasis

In a double-blind, placebo-controlled trial, 256 immunocompromised patients, most of whom were HIV-positive with biopsy-proven esophageal candidiasis, were randomized to voriconazole (400 mg for one dose; then 200 mg twice daily), fluconazole (400 mg for one dose; then 200 mg daily), or placebo. The study evaluated efficacy, tolerability, and safety.[153] Patients were on therapy for at least seven days after clinical signs and symptoms resolved or for a maximum of six weeks. Patients underwent endoscopy at day 43 to determine efficacy. Endoscopy-documented success (98.3 percent versus 95.1 percent, respectively), as well as symptomatic success (88 percent versus 91.1 percent, respectively), was similar between voriconazole and fluconazole. Visual disturbances were reported in 18 percent of voriconazole patients compared to five percent with fluconazole. More patients discontinued voriconazole due to laboratory abnormalities or treatment-related adverse effects.

griseofulvin oral suspension and terbinafine granules (Lamisil Granules) – tinea capitis

A prospective, non-blinded, cross-sectional study of three commonly used drugs (terbinafine, griseofulvin, and fluconazole) was undertaken in children aged 12 years and younger, presenting to a pediatric superspecialty hospital. The comparative efficacies of these three drugs were evaluated. [154] A total of 75 patients (25 in each treatment group) who completed the designated treatment protocol were included in the final analysis. Of these, 60 percent had non-inflammatory tinea apitis (TC) and 56 percent had an ectothrix pattern on hair microscopy. Trichophyton violaceum was the most commonly isolated fungus. Cure rates of 96, 88, and 84 percent were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of TC. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications.

Terbinafine oral granules and griseofulvin oral suspension were compared for efficacy and safety in the treatment of tinea capitis in children ages four to 12 years in two investigator-blinded studies.[155]

Patients were randomized to terbinafine 5-8 mg/kg daily or griseofulvin 10-20 mg/kg for six weeks of treatment. The 1,549 patients were followed for an additional four weeks. End of study complete cure was defined as a negative fungal culture and microscopy with no symptoms. Mycologic cure was defined as negative fungal culture and microscopy. Clinical cure was the absence of symptoms. The pooled intent-to-treat population consisted of 1,286 patients. Rates of complete cure and mycologic cure were significantly higher for terbinafine than for griseofulvin (45.1 versus 39.2 percent and 61.5 versus 55.5 percent, respectively; each $p<0.05$). Most griseofulvin patients (86.7 percent) received 10 to 19.9 mg/kg per day; complete cure rate was not found to be higher among patients who received more than griseofulvin 20 mg/kg per day compared with those who received less than 20 mg/kg per day. Complete cure rate was statistically significantly greater for terbinafine compared to griseofulvin in trial 1 (46.23 versus 34.01 percent, respectively) but not in trial 2 (43.99 versus 43.46 percent, respectively). Clinical cure was similar between the two drugs based on the pooled data. Subgroup analyses revealed that terbinafine was significantly better than griseofulvin for all cure rates among patients with *Trichophyton tonsurans* but not *Microsporum canis* ($p<0.001$). For *M. canis*, mycologic and clinical cure rates were significantly better with griseofulvin than with terbinafine ($p<0.05$). Therapies were well tolerated.

miconazole (Oravig) versus clotrimazole troches

In a randomized, double-blind, double-dummy trial, miconazole buccal 50 mg tablets daily were compared to clotrimazole 10 mg troches five times daily for 14 days in 577 HIV-positive patients with oropharyngeal candidiasis.[156,157] Patients were required to have symptoms and microbiological documentation of candidiasis for study entry. Clinical cure was defined as a complete resolution of signs and symptoms of oropharyngeal candidiasis at the test-of-cure visit (days 17-22). Clinical cure was achieved in 61 percent of miconazole patients compared to 65 percent of clotrimazole patients (p=NS) in the intent to treat population. Clinical relapse occurred in 27.3 and 27.8 percent of patients, respectively. Mycological cure (eradication of *Candida* on days 17-22) occurred in 27.2 and 24.7 percent of patients, respectively. Adverse events were similar between treatments.

terbinafine (Lamisil) versus itraconazole (Sporanox) - onychomycosis

In a prospective, randomized, double-blind, multicenter study, researchers compared the efficacy and tolerability of continuous terbinafine with intermittent itraconazole for treatment of toenail onychomycosis.[158] The study included 496 patients diagnosed with toenail onychomycosis caused by a dermatophyte. Patients were randomly assigned to four parallel groups: terbinafine 250 mg per day for 12 or 16 weeks or itraconazole 400 mg per day for one week in every four weeks for 12 or 16 weeks. The primary outcome measure was mycological cure, defined as negative microscopy and negative culture of samples from the target toenail. At week 72, mycological cure rates were 75.5 percent in the 12-week terbinafine group and 80.8 percent in the 16-week terbinafine group, compared with 38.3 percent in the itraconazole 12-week study group and 49.1 percent in the itraconazole 16-week group. All treatments were well tolerated, with no significant differences in the number or type of adverse events reported. Researchers concluded continuous terbinafine is more effective than intermittent itraconazole for the treatment of toenail onychomycosis.

In a five-year, blinded, prospective follow-up study to the aforementioned study, the long-term effectiveness of terbinafine was compared to itraconazole in 151 patients.[159] At the end of five years, mycologic cure achieved with one treatment course was found in 46 percent and 13 percent of the terbinafine-treated and itraconazole-treated patients, respectively ($p<0.001$). Mycologic and clinical

relapse rates were significantly higher in the itraconazole-treated group, 53 percent and 48 percent, respectively, compared to the terbinafine-treated group, 23 percent and 21 percent, respectively.

A prospective, investigator-blinded, long-term follow-up (1.25 to seven years) study comparing four treatment regimens with itraconazole and terbinafine was conducted.[160] The four regimens were either terbinafine continuous, intermittent, or in combination with itraconazole, and pulsed itraconazole. Recurrence rate of onychomycosis was the outcome used to determine which of the four regimens was the most effective at decreasing the rate of re-infection. Although no statistical significance was found between the dosing regimens, it was determined that itraconazole therapy was associated with higher rates of recurrence (59 percent) than was terbinafine regimens (32 percent recurrence rate for continuous and 36 percent for intermittent). Combining the two drugs did not reduce the rate of recurrence of the infection as compared to monotherapy (57 percent rate of recurrence of infection for combination therapy).

itraconazole (Onmel) versus itraconazole (Sporanox) - onychomycosis

The efficacy of itraconazole (Onmel) for the treatment of onychomycosis of the toenail was evaluated in a 12-week, randomized, placebo-controlled, third-party blinded, multicenter trial comparing one 200 mg Onmel tablet to two 100 mg itraconazole capsules and placebo once daily tablets, in 791 patients.[161] The primary endpoint of Complete Cure at Week 52, nine months after completion of study medication, was 22.3 and one percent, for Onmel and placebo, respectively. The Mycologic Cure rate was 44 percent and the Clinical Cure rate was 26 percent for subjects treated with Onmel. The Mycological Cure rate was six percent and the Clinical Cure rate was three percent for subjects treated with placebo. Efficacy results comparing a single 200 mg Onmel tablet to 200 mg of itraconazole capsules (two 100 mg capsules) were similar.

posaconazole (Noxafil), fluconazole (Diflucan) and/or itraconazole (Sporanox)

Due to the lack of other comparative data with posaconazole, this study is included in the review. In a randomized, multicenter study, safety and efficacy of posaconazole (n=304), fluconazole (n=240), and itraconazole (n=58) were compared for invasive fungal infection prophylaxis in patients with prolonged neutropenia.[162] Patients were undergoing treatment for acute myelogenous leukemia or myelodysplastic syndrome. In this investigator-blinded study, patients received prophylaxis with the assigned treatment with each cycle of chemotherapy until recovery from neutropenia and complete remission occurred or until the occurrence of an invasive fungal infection or for up to 12 weeks. Proven or probable invasive fungal infections were reported in two percent of the posaconazole group and eight percent in the fluconazole or itraconazole group (absolute reduction, 6 percent; 95% CI, -9.7 to -2.5; $p<0.001$). Invasive aspergillosis was significantly lower in the posaconazole group (one percent versus seven percent, $p<0.001$). Survival was significantly higher in the posaconazole group (16 percent mortality) than in the fluconazole/itraconazole group (22 percent mortality, $p=0.04$). Serious adverse effects were significantly more common in the posaconazole group (six percent versus two percent; $p=0.01$). The most common adverse effects related to the gastrointestinal tract.

In a multicenter, randomized, double-blind trial, oral posaconazole and fluconazole were compared for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy.[163] Six hundred allogenic hematopoietic stem-cell transplant patients were enrolled. At the end of the 112-day treatment period, posaconazole and fluconazole were similarly effective in preventing all invasive fungal infections (5.3 and 9 percent,

respectively; odds ratio=0.56; 95% CI, 0.30 to 1.07, p=0.07). Posaconazole was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3 and 7 percent, odds ratio=0.31, 95% CI, 0.13 to 0.75, p=0.006). Overall mortality was similar in the two groups; however, the number of deaths from invasive fungal infections was lower in the posaconazole group (1 and 4 percent, p=0.046). Treatment-related adverse effects were similar in both groups (36 percent for posaconazole and 38 percent for fluconazole).

Due to the lack of other comparative data with posaconazole, this study is included in the review. Posaconazole was compared to fluconazole in a multicenter, randomized, single-blinded trial evaluating efficacy and safety in the treatment of oropharyngeal candidiasis in patients with HIV/AIDS.[164] Patients (n=350) were randomized to posaconazole or fluconazole 200 mg on day one then 100 mg daily for 13 days. Clinical success, defined as cure or improvement on day 14, was observed in 91.7 and 92.5 percent for posaconazole and fluconazole groups, respectively (95% CI, -6.61 to 5.04). Mycological success was 68 percent in both arms on day 14, but mycological success on day 42 was 40.6 and 26.4 percent for posaconazole and fluconazole, respectively (p=0.038). Clinical relapse rates were 31.5 percent for posaconazole and 38.2 percent for fluconazole. Adverse effects were similar.

isavuconazole (Cresemba) versus voriconazole (Vfend)

A randomized, double-blind, non-inferiority active controlled trial which evaluated the safety and efficacy of isavuconazole (Cresemba) versus voriconazole for the primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi was conducted. [165] Each treatment group included n=258 patients. Patients randomized to receive isavuconazole (Cresemba) treatment were administered an IV loading dose of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every eight hours for the first 48 hours. Beginning on day 3, patients received IV or oral therapy of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily. Patients randomized to receive voriconazole treatment were administered voriconazole IV with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by 4 mg/kg IV every 12 hours for the following 24 hours. Therapy could then be switched to an oral formulation of voriconazole at a dose of 200 mg every 12 hours. In this trial, the protocol-defined maximum treatment duration was 84 days. Mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by an intravenous route of administration. Results for overall success at end of treatment were 35 percent of isavuconazole (Cresemba) treated patients compared to 38.9 percent of voriconazole-treated patients.

META-ANALYSIS

A meta-analysis determined mycological cure rate in randomized clinical trials is consistently 76 percent for terbinafine (Lamisil) and 63 percent for pulse dose itraconazole (Sporanox).[166] Thirty-six randomized, controlled trials evaluated the efficacy of terbinafine, itraconazole, fluconazole (Diflucan), and griseofulvin (Grifulvin V, Gris-PEG) in the treatment of dermatophyte toenail onychomycosis. Studies were required to use a standard dosage regimen (pulse or continuous), treatment duration, and follow-up period. Mycological and clinical response rates were compared for the randomized controlled trials and open trials for each of the agents. Studies were pooled from earliest (1966) to most recent to determine the cumulative meta-analytical average. The overall cumulative meta-average for mycological cure rates were terbinafine 76 ± 3 percent (18 studies), itraconazole pulse 63 ± 7 percent (six studies), itraconazole continuous 59 ± 5 percent (seven studies), fluconazole 48 ± 5 percent (three studies), and griseofulvin 60 ± 6 percent (three studies). When comparing randomized

controlled trials and open-label trials, the cumulative meta-analytical average for mycological cure rates were significantly higher in the open-label trials for terbinafine, itraconazole pulse dose, and fluconazole.

Randomized controlled trials (21 studies) that evaluated systemic antifungal therapy for tinea capitis in immunocompetent children (n=1,812) were identified.[167] All studies required a tinea capitis diagnosis to be confirmed by microscopy or growth of dermatophytes in culture or both. For infections caused by *Trichophyton* species, terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy (RR 1.09; 95% CI, 0.95 to 1.26). Two studies found cure rates to be similar following treatment with itraconazole and griseofulvin for six weeks. There was no difference between itraconazole and terbinafine for treatment periods lasting two to three weeks in two studies involving 160 children (RR 0.93; 95% CI, 0.72 to 1.19). Two studies that included 140 children found similar cure rates between two to four weeks of fluconazole with six weeks of griseofulvin (RR 0.92; 95% CI, 0.8 to 1.05). For *Microsporum* infections, no significant difference in cure rates were observed between terbinafine and griseofulvin, based on one small study of 29 children (RR 0.64; 95% CI, 0.19 to 2.20). Shorter treatment durations may improve treatment adherence.

A meta-analysis compared griseofulvin (Grifulvin V, Gris-PEG) and terbinafine in the treatment of tinea capitis in children.[168] Randomized, clinical studies with treatment for at least six weeks were included. Identification of the dermatophyte was required for inclusion. A total of six trials were evaluated. Outcome parameters were compared at 12 to 16 weeks after enrollment. The common odds ratio was 0.86, which tells us that the studies included had similar outcomes. When *Trichophyton* species were isolated in studies looking at outcomes at 12 weeks, the results trended toward terbinafine. Outcomes after eight weeks for both treatments were similar. Authors concluded terbinafine for two to four weeks is at least as effective as griseofulvin for at least six weeks for *Trichophyton* infections of the scalp. With other pathogens, griseofulvin may be a superior agent.

Another meta-analysis evaluated seven trials with griseofulvin for the treatment of tinea capitis. Overall cure rate after four to six weeks post-treatment was 73.4 percent (seven studies; n=438 patients).[169] Higher efficacy rates were reported with the use of higher dosages of griseofulvin (>18 mg/kg/day). When broken down by species, the mean efficacy for *Trichophyton* and *Microsporum* were 67.6 percent (five studies, n=396) and 88.1 percent (two studies, n=42 patients), respectively.

A meta-analysis was conducted comparing griseofulvin to terbinafine in cases of tinea capitis. The objective was to determine whether there is a statistically significant difference in efficacy between the drugs for a given dose and duration (8 weeks of griseofulvin [6.25-12.5 mg/kg/day] to 4 weeks of terbinafine [3.125-6.25 mg/kg/day]), and to determine if a genus-specific difference exists. Based on the Mantel-Hansel method the odds ratios (OR) with 95 percent confidence intervals did not find a significant difference in the overall efficacy of the two agents, but there was efficacy differences based on species of infection. When the causative species was *Microsporum*, griseofulvin was superior (p=0.04), when the causative species was *Trichophyton*, terbinafine was superior (p=0.04).[170]

A Cochrane review found very few comparative trials on which to evaluate efficacy of prophylaxis of oropharyngeal candidiasis in HIV-positive patients.[171] It appeared that ketoconazole, fluconazole, itraconazole, and clotrimazole improved treatment outcomes in the treatment of oropharyngeal candidiasis. An update was performed evaluating clinical trials performed between 2005 and 2009.[172] Five additional studies were identified. Only one study was performed in children; therefore, little evidence exists. For adults, very few comparative trials for each comparison exist. Due to insufficient

evidence, no conclusion could be made about the effectiveness of clotrimazole, nystatin, amphotericin B, itraconazole, or ketoconazole with regard to oropharyngeal candidiasis prophylaxis.

A meta-analysis completed in 2011 reviewed itraconazole recurrence rates as compared to terbinafine recurrence rates. This analysis concluded that itraconazole had a higher rate of onychomycosis recurrence than did terbinafine.[173]

SUMMARY

Oral antifungal agents are useful in the treatment of a variety of infections in both the immunocompetent and immunocompromised patient. Oral antifungals used in the outpatient setting generally treat fungal infections such as oropharyngeal candidiasis, urinary tract infections, superficial skin infections, and onychomycosis. Due to its excellent penetration into many tissues, fluconazole (Diflucan) is effective Candida treatment for a variety of infections, lacking concerns about pH-dependent absorption such as that seen with ketoconazole (Nizoral). Effective therapy for oropharyngeal candidiasis includes fluconazole, itraconazole, ketoconazole, nystatin, and clotrimazole troches (Mycelex). Voriconazole (Vfend) has been shown to have similar efficacy to fluconazole in the treatment of esophageal candidiasis; however, more adverse effects are reported with voriconazole. Posaconazole (Noxafil) oral suspension has an indication for treatment of oropharyngeal candidiasis when refractory to itraconazole and/or fluconazole. Nystatin is also used to treat intestinal candidiasis and may be used in infants and children.

In comparative trials, terbinafine (Lamisil) demonstrated higher treatment success rates of toenail onychomycosis in immunocompetent patients compared to itraconazole (Sporanox). Terbinafine also demonstrated higher clinical success rates in the treatment of tinea capitis than griseofulvin (Grifulvin V, Gris-PEG); however, griseofulvin had higher success rates in those infections caused by *Microsporum*.

Utility of griseofulvin for treatment of onychomycosis has decreased since the introduction of the azole antifungals and terbinafine. Duration of therapy is often longer than with other agents, which may result in increased adverse effects and require monitoring of liver, renal, and hematopoietic function. However, griseofulvin is still a useful agent in the treatment of many fungal skin infections that do not respond to topical therapies.

For serious fungal infections, isavuconazonium, posaconazole, flucytosine (Ancobon), voriconazole, itraconazole, and fluconazole have indications for the treatment and/or prophylaxis of various serious fungal infections.

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